THE RÔLE OF THE THYROID IN THE REGULATION OF THE BLOOD CHOLESTEROL OF RABBITS

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The important rôle of the thyroid in cholesterol metabolism has recently become recognized, although the regulatory mechanisms involved are little understood. It seemed desirable to study further the effect of thyroidectomy on the regulation of the blood cholesterol level in rabbits and to re-examine and amplify previous observations (1–3).

The present report deals with the effect of thyroidectomy on the blood cholesterol values of otherwise normal rabbits, of rabbits with hypercholesterolemia, and of rabbits that did not respond to cholesterol feeding with a rise in blood cholesterol, that is, the so called resistant group. Furthermore, comparisons have been made between the action of thyroxin, potassium iodide, and insulin on the hypercholesterolemia of intact and thyroidectomized rabbits fed cholesterol. Emphasis has been placed upon the individual variations of the blood cholesterol of a relatively few rabbits, rather than upon a comparison of the average values of large groups of animals with less frequent blood determinations. In studying the effects of various substances on the level of the blood cholesterol, animals with a long standing, fairly stabilized hypercholesterolemia have again been used. It is believed that any change is more accurately reflected by this method than by using rabbits with a normal blood cholesterol or rabbits fed cholesterol and some agent concurrently in an attempt to modify an expected, but nevertheless hypothetical, rise in the blood cholesterol.

Methods

Dutch belted rabbits were used exclusively. They were 6 months old when received, with a few exceptions noted below. The animals were kept in individual cages indoors and fed a stock diet of oats and green vegetables. Aside from the first group reported below, each rabbit was given 1 gm. of crystalline cholesterol mixed with the moistened grain three times a week throughout the experiments.

Blood was obtained from an ear vein at weekly intervals during the preliminary feeding periods and in the intervals between experiments but more frequently during the times that the various measures were being carried out. The cholesterol was determined on the whole blood by the method of Bloor, Pelkan, and Allen (4). The same rabbit was often used for several different observations. Thus, the influence of thyroidectomy and of the administration of thyroxin, potassium iodide, and insulin with appropriate intervals between each series of observations may have been determined on a single animal.

The thyroid ablations were performed under ether anesthesia. A midline incision was made over the larynx and trachea and the glands exposed. They were then dissected out as carefully as possible to ensure complete removal. Bleeding was easily controlled by pressure. At the conclusion of the experiments an autopsy was performed and the absence of thyroid tissue verified. In 4 animals it was found that removal had been incomplete and regeneration had occurred. These animals are treated separately in the following sections.

Effect of Thyroidectomy on Blood Cholesterol of Normal Rabbits

A significant increase in the blood cholesterol of rabbits has been noted after thyroidectomy by several observers (5–9), while one investigator (10) reported that no rise occurred and another (11) that it was temporary. In a previous communication (2) it was pointed out that the general level of the blood cholesterol of a group of thyroidectomized rabbits observed for 110 days after operation was only slightly higher than that of a control group of normal animals. The average blood cholesterol of the normal group for the whole period was 110 mg. and of the thyroidectomized 121 mg.

Before going ahead with work involving the use of thyroid ablation, it seemed advisable to repeat our previous observation but this time comparing the blood cholesterol before and after operation in the same animals rather than in separate groups of animals.

The blood cholesterol was determined weekly in each of 6 rabbits for 5 weeks before and for a similar period after thyroidectomy. During this whole time the animals were kept on a normal diet without added cholesterol. The complete removal of the thyroids was verified at a later date at autopsy.

The results are shown in Table I. The blood cholesterol of each rabbit increased after thyroidectomy. This increase was not marked and ranged from 10 to 28 per cent for the 5 week period for the individual animal. For the entire group the preoperative average was 114 mg. Postoperatively it was 136 mg., a rise of 19 per cent.

In conclusion, it seems that in the 5 weeks following thyroidectomy the blood cholesterol of a rabbit not fed cholesterol is slightly higher than during the control period.

TABLE I

Effect of Thyroidectomy on Blood Cholesterol of Normal Rabbits

Rabbit No.	Blood cholesterol, *mg. per 100 cc.*												Increase
	Weeks before thyroidectomy						Weeks after thyroidectomy						
	5	4	3	2	1	Average	1	2	3	4	5	Average	
													per cent
1-91	117	104	110	98	123	110	142	129	114	114	117	123	+12
2-21	124	123	128	158	129	132	179	162	156	139	158	159	+20
2-24	101	91	111	110	113	105	144	117	158	116	136	134	+28
2-25	92	107	112	112	108	106	117	132	139	140	143	134	+26
2-26	91	94	110	123	111	106	110	99	137	101	132	116	+10
2-33	116	122	119	145	—	126	180	124	169	151	129	151	+20
Average						114						136	+19

Effect of Thyroidectomy on Hypercholesterolemia of Rabbits

The next step was to determine the effect of thyroidectomy on the hypercholesterolemia of rabbits that had been fed cholesterol over a considerable period of time. Here again the effect of the operation was judged by comparing the level of the cholesterol in the blood of the same rabbit before and after the thyroid ablation.

There were 8 rabbits in the group. 5 were males and 3 females. They had been fed cholesterol for a period of 3 to 13 months before operation, and all had a hypercholesterolemia. Complete removal of the thyroid was verified at autopsy at a later date in 7 rabbits, while in 1 (No. 3-53) partial regeneration was found to have taken place when examined 7 months postoperatively.

The effect of thyroidectomy on the already high blood cholesterol is shown in Table II. In each instance a prompt, substantial rise

occurred that surpassed the previously recorded high for the animal. The maximal increase during a period of 2 months after the operation varied from 74 to 255 per cent and averaged 137 per cent for the group.

The subsequent course of the blood cholesterol of these rabbits after establishing a new high varied. In general it can be said that the postoperative rise was maintained or gradually increased in 3 animals; was followed by a slight fall and then a later rise to new high levels in 2; and was temporary in 3 with a return to preoperative levels. In the last group was the animal found to have thyroid regeneration at autopsy 7 months after operation.

TABLE II

Effect of Thyroidectomy on Blood Cholesterol of Cholesterol-Fed Rabbits

Rabbit No.	Sex	Duration cholesterol feeding	Blood cholesterol, *mg. per 100 cc.*									Maximal increase
			Previous high	Preoperative level	Weeks postoperative							
					1	2	3	4	5	6	7	8	
		mos.											*per cent*
3-06	M	11	305	281	472	850	833	819	834	781	834	835	203
3-39	M	10	616	616	—	1170	1030	1560	1230	1170	1010	—	153
3-49	F	12	1170*	670	—	1080	1170	1200	902	694	738	—	79
3-51	F	6	362	358	568	675	726	610	532	400	403	521	89
3-52	M	13	762	738	—	1115	1285	1145		Died			74
3-53	M	6	333	305	397	417	385	526	500	438	556	500	82
3-56	F	13	794	690	—	1145	1065	1510	1035	705	695	—	119
3-65	M	3	232	220	782	660	638	399	430	387	361	538	255
Average													137

* Single determination; otherwise not above 736 mg.

In summary, thyroidectomy in the cholesterol-fed rabbit with hypercholesterolemia is followed by a further rise in the level of the blood cholesterol. This rise is usually maintained, but in a minority may be temporary. The magnitude of the increase is in sharp contrast to the insignificant rise that occurs following this operation in the rabbit on a normal diet without cholesterol.

Effect of Thyroidectomy on Blood Cholesterol of Resistant Rabbits

It is a common experience for anyone who has fed cholesterol to large groups of rabbits to find that certain animals do not develop a

high blood cholesterol despite an apparently adequate cholesterol intake over a sufficiently protracted feeding period. These animals are said to be resistant to the effect of cholesterol on the blood, and in that respect they react like carnivores or omnivores. Because of the striking effect of thyroidectomy in causing a further rise in the hypercholesterolemia of cholesterol-fed rabbits, it was decided to subject such resistant rabbits as were available to thyroidectomy in an attempt to destroy this resistance and cause them to react as herbivores by responding to cholesterol feeding with a rise in the level of the cholesterol in the blood.

TABLE III

Effect of Thyroidectomy on Blood Cholesterol of Cholesterol-Fed Resistant Rabbits

Rabbit No.	Sex	Duration cholesterol feeding	Blood cholesterol, *mg. per 100 cc.*										Maximal increase
			Previous high	Preoperative level	Weeks postoperative								
					1	2	3	4	5	6	7	8	
		mos.											*per cent*
2-59	M	7	192	125	179	281	305	333	313	260	263	301	166
3-37	F	3	154	120	164	167	130	137	195	190	195	272	127
3-38	M	3	145	122	198	217	232	250	278	227	200	333	165
3-64	M	4	284*	171	203	176	253	312	309	334	373	—	118
3-67	M	3	125	117	151	206	221	214	242	243	235	234	108
3-74	M	3	258*	168	798	837	852	694	494	670	893	999	495
3-77	F	3	171	171	606	726	1290	1390	1250	1235	1130	1115	713
Average													270

* On one occasion; other determinations below 200 mg.

There were 7 rabbits available that had been fed cholesterol for from 3 to 7 months and had failed to develop a blood cholesterol exceeding 200 mg. except for a single determination in each of 2 animals. At the time of operation the blood cholesterol in the group ranged from 117 to 171 mg. 5 of the animals were males and 2 were females. The high incidence of males among the resistant animals has been previously noted (12). Following operation cholesterol feeding was continued as before.

Table III shows the results of the blood cholesterol determinations for the 2 months following thyroidectomy. In each case there occurred a marked increase in the blood cholesterol which was evident as a rule immediately after the operation. The maximal increase

varied from 108 to 713 per cent with an average of 270 per cent. In no case did the blood cholesterol revert later to its previous level.

In summary, the ablation of the thyroid destroys the resistance that certain cholesterol-fed rabbits show to the development of a hypercholesterolemia. This result is of great theoretical interest.

Effect of Thyroidectomy on Response to Thyroxin

It has been well established that thyroid extract or thyroxin will lower the blood cholesterol of rabbits. This effect is particularly striking when cholesterol-fed animals with a hypercholesterolemia are used (3). There were at least two objections to this last report, however. In the first place, infrequent determinations of the cholesterol prevented a realization of the magnitude of the fall in the blood; secondly, the thyroid was fed to the rabbits concurrently with cholesterol for a 3 week period, which naturally gave less clear cut results than would be obtained by giving a single large dose of thyroxin. The present work was undertaken to correct these defects and furthermore to compare the type of response of normal and thyroidectomized animals to a single dose of thyroxin.

11 rabbits with thyroids intact were used. There were 5 males and 6 females. 3 of the animals (Nos. 2-56, 2-57, and 2-60) were 2 to 3 years old at the beginning of the feeding period; the others were the usual 6 months of age. They had been fed cholesterol for from 7 to 15 months, and all had a hypercholesterolemia that had been at a fairly constant level for the individual for weeks or months before the experiment was started. On the day the experiment was begun a control blood was taken about 9 a.m., and at 10 a.m. the rabbit was given a subcutaneous injection of 1.2 mg. of crystalline thyroxin dissolved in N 50 sodium hydroxide. Another blood was taken for cholesterol determination in the late afternoon, then twice daily for several days and with decreasing frequency thereafter. Cholesterol feeding was continued throughout the experiment.

The results are shown in Table IV. A substantial decrease in the level of the blood cholesterol occurred in each animal. The maximal drop varied from 25 to 64 per cent with an average of 40 per cent. The lowest point was usually reached on the 3rd or 4th day, but occasionally on the 2nd or 5th day. Following this drop, the cholesterol then rose steadily to its previous level which was usually attained by the 5th to 9th day but was delayed in one instance until

TABLE IV

Effect of Thyroxin on the Hypercholesterolemia of Intact Rabbits

Rabbit No.	Sex	Duration cholesterol feeding	Blood cholesterol, *mg. per 100 cc.*																		Maximal decrease
			Days																		
			1			2		3		4		5	6	7	8	9	10–11	12–13	14–15	16–18	19–21	
			a.m.		p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.											
		mos.																				*per cent*
2-51	F	11	538	Thyroxin injected	463	420	316	—	—	—	—	368	407	435	472	480	491	473	463	500	532	41
2-52	F	11	521		455	417	365	—	—	—	—	394	427	463	495	520	532	556	633	666	658	30
2-53	F	9	550		522	472	410	390	—	417	—	450	468	510	500	481	—	521	—	—	—	29
2-54	M	11	329		313	291	266	238	217	255	—	325	—	385	373	373	Died					37
2-55	M	11	250		219	192	177	152	128	179	—	189	—	214	225	260	263	—	250	—	284	49
2-56	F	7	338		325	278	—	255	—	245	—	245	—	313	—	347	357	—	417	385	373	28
2-57	M	9	388		370	333	290	290	—	345	—	382	376	391	400	416	—	419	—	—	—	25
2-60	F	7	455		466	397	—	333	—	301	—	294	—	368	—	463	520	—	520	500	481	35
3-08	M	15	682		682	507	458	395	323	375	387	615	670	—	852	—	1020	—	838	788	—	53
3-40	M	9	1090		834	756	—	580	466	387	411	443	530	—	860	—	1115	1130	938	986	1170	64
3-57	F	9	375		300	206	171	—	—	171	206	295	—	576	646	735	780	852	938	—	—	54
Average																						40

the end of the 3rd week. In 3 of the rabbits the original level of the blood cholesterol was exceeded during this rise. For example, No. 3-57, that had never had a blood cholesterol above 375 mg. in 9 months of feeding, showed a drop in cholesterol values to 171 mg. after thyroxin, then rose to 576 mg. on the 7th day, and had reached 938 mg. on the 15th day.

For comparison with the foregoing, a group of 11 thyroidectomized rabbits was used. 7 were males and 4 females. After 6 to 18 months of cholesterol feeding, the animals all had a hypercholesterolemia which was more marked than in the group with thyroids intact. This was due in part at least to the further rise of blood cholesterol that occurs after thyroidectomy which had been performed in these animals 3 to 10 months before. Thyroid removal was proved at autopsy to have been complete in 7 rabbits, but in 4 thyroid regeneration had taken place when an autopsy was done 1 to 3 months after the conclusion of the experiment. These animals are grouped separately in the table and listed as having had a partial thyroidectomy. Thyroxin was injected and blood cholesterol determinations made as in the intact animals.

The results are shown in Table V. As in the animals with thyroids a decrease in the blood cholesterol occurred soon after the injection of thyroxin. The maximal drop amounted to 44 to 70 per cent with an average of 61 per cent for the animals in which the thyroidectomy was complete, and was practically the same for those with an incomplete thyroidectomy, ranging from 49 to 65 per cent and averaging 60 per cent. This was a greater decrease than occurred in the rabbits with thyroid glands intact. How much this was due to an inherent difference in response between animals with and without thyroids cannot be said from this small series, but it seems probable that it was due in part at least to the higher original levels of the blood cholesterol of the thyroidectomized animals. As in the intact group, the low point of the blood cholesterol was usually reached on the 3rd or 4th day, but occurred on the 2nd day in 1 and on the 5th day in 2. The cholesterol returned to its original value in a widely variable time in 7 of the animals, and continued to higher levels in 3 of these. In 3 rabbits the blood cholesterol remained permanently below its original level.

One rabbit was given an injection of N 50 sodium hydroxide without thyroxin as a control. No change in the blood cholesterol resulted.

TABLE V

Effect of Thyroxin on the Hypercholesterolemia of Thyroidectomized Animals

Rabbit No.	Sex	Duration cholesterol feeding	Interval since operation	Blood cholesterol, *mg. per 100 cc.*																				Maximal decrease
				Days																				
				1			2		3		4		5		6	7	8	9	10–11	12–13	14–15	16–18	19–21	
				a.m.		p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.										
		mos.	*mos.*																					*per cent*
Rabbits with Total Thyroidectomy																								
3-06	M	18	7	1135	Thyroxin injected	1070	860	862	694	750	670	601	518	436	—	551	597	524	527	—	656	1065	1055	62
3-37	F	13	10	1155		1010	694	528	481	375	347	—	544	—	702	938	—	1210	—	1645	1880	1805	1645	70
3-38	M	9	6	1340		—	938	—	675	604	514	475	575	660	816	—	876	—	902	910	756	789	1040	65
3-39	M	13	3	1305		1155	1090	977	860	782	782	727	794	—	816	Died								44
3-51	F	11	5	816		670	577	431	383	276	387	—	—	—	636	—	852	—	—	852	—	684	675	66
3-56	F	16	3	981		808	629	500	487	431	469	500	577	625	646	—	750	920	928	1110	—	1200	1220	56
3-65	M	6	3	994		762	714	572	452	350	364	354	475	452	507	—	682	852	938	1068	766	781	845	65
Average																								61
Rabbits with Partial Thyroidectomy																								
3-53	M	10	4	300		265	214	154	—	—	276	280	375	—	—	568	536	446	469	507	481	582	670	49
3-67	M	6	3	329		308	272	223	226	117	132	169	171	160	259	—	266	298	301	295	274	274	276	64
3-74	M	6	3	750		694	528	481	387	307	284	—	—	—	352	412	458	—	450	463	—	552	—	62
3-77	F	6	3	1265		1200	1130	876	700	634	528	552	521	528	530	—	441	524	621	766	822	928	902	65
Average																								60

In summary, it seems evident that a single injection of thyroxin is capable of producing a significant drop in the blood cholesterol of rabbits with hypercholesterolemia, regardless of whether the thyroid glands are intact or have been partially or completely removed. The maximal effect is usually evident on the 3rd or 4th day after injection.

Effect of Thyroidectomy on Response to Potassium Iodide

Potassium iodide when administered in large doses concurrently with cholesterol has been shown to prevent the development of a hypercholesterolemia and the resultant formation of atheromatous lesions in the aorta (1). This protective action was found to be abolished in thyroidectomized rabbits (2), suggesting that the iodide acted in some way through the thyroid. It was later shown that when potassium iodide was given to rabbits with a high blood cholesterol due to long continued cholesterol feeding, a further increase in the hypercholesterolemia occurred (3). This result was unexpected and suggested that the iodide might be mobilizing cholesterol from the tissues, resulting in an increase in the amount in the circulating blood, but further work did not confirm this hypothesis (12). It was of interest to determine whether the action of KI in causing increase in a blood cholesterol already high was also dependent upon the presence of the thyroid, or whether, possibly, some other mechanism was involved.

6 intact rabbits with a hypercholesterolemia due to cholesterol feeding of from 9 to 19 months' duration were each given a gram of potassium iodide as an aqueous solution mixed with the grain three times a week for 2 weeks. KI was then discontinued but the cholesterol feeding was carried on as usual.

The results are shown in Table VI. As had been found before (3), a definite rise in the level of the blood cholesterol occurred in 5 of the 6 animals. With the exception of the one animal whose blood was unchanged, the average increase for the group was 44 per cent, ranging from 14 to 74 per cent. For the entire group of 6 rabbits the increase averaged 37 per cent. The rise tended to occur in an irregular fashion and a definite peak was often not demonstrable. This type of effect is in sharp contrast to that of thyroxin.

TABLE VI

Effect of Potassium Iodide on Hypercholesterolemia of Intact Rabbits

Rabbit No.	Sex	Duration cholesterol feeding	Blood cholesterol, *mg. per 100 cc.*																				Maximal increase
			Previous high	Control		Days																	
						2	4	6	8	10	12	14		16	18	20	22	24	26	28	30	32	34	
		mos.			KI feeding begun								KI feeding stopped											*per cent*
3-08	M	16	1020	852		722	638	670		638	786	816		876		782		678						None
3-40	M	10	1170	1090		1065	1040		1130	1445	1270	1350		1115	1270		1590	1220	1235	1140	893	1130	1040	46
3-57	F	10	938	904		876		920	1065	1100	1170	1250			1080	1065						1270		40
3-36	F	19	860	860		1090	1160	1250		1050	893	977		844	860	920		700	560	568				45
3-47	M	18	852	656		716	884	920		966	938	1105		860	1065	1105		870	1140	1135				74
3-68	M	9	1080	762		853	845	868		733	822	822		674	674	598		545	625	610				14
Average																								44

For comparison with these rabbits with intact thyroids, there were 10 animals shown later at postmortem examination to have been completely thyroidectomized and 4 in which the thyroidectomy was incomplete. In this total group of 14 were 9 males and 5 females. When the experiment was begun, the animals had been fed cholesterol for a period of 3 to 16 months, and had been thyroidectomized 1 to 8 months. Cholesterol feeding was continued throughout. Each rabbit was given 1 gm. of potassium iodide three times a week for 2 weeks.

The results are shown in Table VII. All the rabbits responded to the potassium iodide feeding with an increase in their existing hypercholesterolemia amounting to from 34 to 122 per cent. The average for those rabbits having no thyroid tissue was 85 per cent, and for those in which thyroidectomy had been incomplete it was 50 per cent. The peak of the increase in the completely thyroidectomized group came usually in the 4th week. In the partially thyroidectomized animals the maximal increase occurred in 2 or 3 weeks.

In summary, the action of potassium iodide in causing a further increase in hypercholesterolemia of cholesterol-fed rabbits is not abolished by thyroidectomy. This is in sharp contrast to the effect of potassium iodide in preventing a rise of blood cholesterol when the drug is given at the beginning of the cholesterol feeding, an effect that is abolished by thyroidectomy. Obviously two different mechanisms are involved.

Effect of Thyroidectomy on Response to Insulin

Because the effect of insulin in lowering blood sugar occurs promptly after injection, it seemed likely that, if there were a concurrent effect on blood cholesterol, this should be manifest in hours rather than in days.

The influence of insulin on blood cholesterol was tested in rabbits with and without thyroids.

The plan followed was to secure a control reading of the cholesterol and sugar in the blood of the animal before injecting insulin and to repeat this determination 2, 4, and 6 hours after the injection. In addition, the blood cholesterol was determined on the 2 days following the insulin. Each rabbit regardless of weight was given 3 units of insulin. From the time the control blood was taken until the sample was obtained 6 hours after insulin the animal was given no food or water.

As a control to the possible effects of insulin injection the diurnal variation in blood cholesterol of 5 fasting rabbits was determined. The results are shown in

TABLE VII

Effect of Potassium Iodide on Hypercholesterolemia of Thyroidectomized Rabbits

Rabbit No.	Sex	Duration of cholesterol feeding	Interval since operation	Blood cholesterol, *mg. per 100 cc.*																					Maximal increase
				Previous high	Control		Days																			
							2	4	6	8	10	12	14		16	18	20	22	24	26	28	30	32	34	
		mos.	*mos.*																						*per cent*
Totally Thyroidectomized Rabbits																									
2-21	F	3	4	467	391				481			544					544				581			747	91
2-25	M	3	4	476	463				495			526					463				625			596	35
3-06	M	16	5	1700	1000		1065	1070		1260	1330	1390	1590		1470	1770		1815	1525	1560	1390	1310	1250		82
3-38	M	10	7	1380	1105		1250	1360		1630	1660	1590	1875		1800	1995		2080	1875	1600	1690	1350	1360	1400	88
3-39	M	11	1	1560	1010		1145		1300		1705	1590			1900		1510		1975		1605		1510	1510	95
3-49	F	14	2	1200	738		660		722		966	957			1040		1170		1510		1280	1400	1400	1210	105
3-51	F	12	6	891	732		651	876	1200		1465	1212	1065		1080		1030		902						100
3-56	F	14	1	1510	695		928		938		1235	1440			1420		1540		1420		1205		1090	1000	122
3-64	M	12	8	1740	1400			1630	1660	1275		1330	1350		1530	1500	1600	1525		1660		1630	1805	1875	34
3-65	M	5	2	782	536			552		762	1040	938	1040			938		948	893	862	910	802	830		94
Average						KI feeding started								KI feeding stopped											85
Partially Thyroidectomized Rabbits																									
3-53	M	11	5	582	577		586		685	758	795	902	988			1040	1040							726	80
3-67	M	5	2	286	286			270		329	326	318	341			364		395	335	278	351	276	300		38
3-74	M	5	2	999	816			695		788	958	646	1160			860		634	625	658	694	658	728		42
3-77	F	5	2	1390	1040			988		1095	1400	1065	1440			1268		1090	1075	1218	1250	1090	1250		38
Average																									50

TABLE VIII

Diurnal Variation in Blood Cholesterol

Rabbit No.	Blood cholesterol, *mg. per 100 cc.*					Maximal variation
	9.00 a.m.	11.00 a.m.	1.00 p.m.	3.00 p.m.	5.00 p.m.	
						per cent
1-87(*a*)	120	107	115	113	110	6
(*b*)	105	105	109	111	116	6
1-93	442	427	437	418	422	3
1-98	124	120	122	116	124	4
1-92	441	431	412	417	452	5
2-31	99	105	99	100	100	4

TABLE IX

Effect of Insulin on Hypercholesterolemia of Intact Rabbits

Rabbit No.		Blood, *mg. per 100 cc.*							Maximal decrease
		Days							
		1					2	3	
		9.00 a.m.	10.00 a.m.	12.00 m.	2.00 p.m.	4.00 p.m.			
									per cent
3-08	Cholesterol	700		658	682	694	568	910	19
	Sugar	107		56	119	113	—	—	
3-36	Cholesterol	528		646	577	586	609	762	Rise
	Sugar	104		62	105	127	—	—	
3-40	Cholesterol	958	3 units of insulin injected	860	860	902	948	950	10
	Sugar	108		87	113	107	—	—	
3-47	Cholesterol	560		595	544	560	636	638	3
	Sugar	91		28	66	104	—	—	
3-61	Cholesterol	738		736	636	614	656	782	17
	Sugar	112		20	79	125	—	—	
3-68	Cholesterol	762		636	646	646	710	882	17
	Sugar	118		42	81	112	—	—	
3-69	Cholesterol	837		727	658	815	694	853	21
	Sugar	101		29	49	94			
Average									15

TABLE X

Effect of Insulin on Hypercholesterolemia of Thyroidectomized Rabbits

Rabbit No.		Blood, *mg. per 100 cc.*							Maximal increase
		Days							
		1					2	3	
		9.00 a.m.	10.00 a.m.	12.00 m.	2.00 p.m.	4.00 p.m.			
									per cent
Totally Thyroidectomized									
3-06	Cholesterol	1100	3 units of insulin injected	1070	992	1000	1155	1090	10
	Sugar	107		54	69	96			
3-37	Cholesterol	988		1055	788	694	938	1250	30
	Sugar	100		63	101	98			
3-38	Cholesterol	1315		1160	1250	1190	1220	1100	16
	Sugar	109		42	66	91			
3-51	Cholesterol	868		750	834	816	705	893	19
	Sugar	106		72	97	108			
3-56	Cholesterol	1130		1115	893	902	1015	962	21
	Sugar	102		25	111	127			
3-65	Cholesterol	837		830	742	652	808	674	22
	Sugar	84		23*	18*	120			
Average									20
Partially Thyroidectomized									
3-53	Cholesterol	536		431	457	431	463	552	20
	Sugar	89		50	61	93			
3-67	Cholesterol	253		212	186	182	Died in convulsions		28
	Sugar	102		22	19*	27*			
3-74	Cholesterol	507		457	371	341	469	452	33
	Sugar	92		29	23*	105			
3-77	Cholesterol	1040		938	920	782	816	824	25
	Sugar	89		32	47	113			
Average									27

* Convulsions.

Table VIII. In 3 animals with a blood cholesterol at normal levels the maximal variation was from 6 to 13 mg. In 2 rabbits with hypercholesterolemia the variation was proportionally no greater. All figures were within the limits of accuracy for the method.

When intact rabbits in possession of their thyroids were injected with insulin a prompt decrease in blood sugar occurred as might be expected. There was also a tendency for the blood cholesterol to fall (Table IX). A decrease amounting to 10 to 21 per cent occurred in 5 of 7 rabbits. The drop in the cholesterol was maximal in 2 hours in 2, and at 4 hours, 6 hours, and 24 hours in the remaining 3. There was no definite correlation between the degree of fall in the blood sugar and blood cholesterol.

For comparison with this group of intact rabbits, 6 animals with thyroids completely removed and 4 partially thyroidectomized were used. As will be noted in Table X a decrease in both the blood sugar and blood cholesterol occurred. Not only did thyroidectomy fail to interfere with this reaction, but, on the contrary, the fluctuations were even more pronounced. 3 of the rabbits developed hypoglycemia convulsions which were fatal in one instance. The blood cholesterol decreased 10 to 33 per cent in each case. In half the rabbits the drop was maximal at 6 hours, while in 2 others the lowest point in the curve was reached at 4 hours.

In summary, insulin causes a decrease in blood cholesterol in rabbits with or without thyroid glands. The fall is somewhat more marked in the absence of the thyroid.

SUMMARY

1. The blood cholesterol of rabbits on a normal diet without added cholesterol is increased only slightly (19 per cent) by thyroidectomy.

2. In rabbits with a hypercholesterolemia due to long continued cholesterol feeding, thyroidectomy causes a marked rise (137 per cent) in the blood cholesterol. This rise is usually maintained.

3. When long continued cholesterol feeding has failed to cause a rise in the blood cholesterol of rabbits, thyroidectomy abolishes this resistance and a hypercholesterolemia is promptly produced.

4. A single injection of thyroxin causes a significant drop in the blood cholesterol of rabbits with hypercholesterolemia. This reaction is not influenced by thyroidectomy.

5. Potassium iodide causes an increase in the blood cholesterol of rabbits with hypercholesterolemia. This reaction is not influenced by thyroidectomy in contrast to the effect of KI in preventing a rise in blood cholesterol when given concurrently from the beginning of cholesterol feeding, an effect which is abolished by thyroidectomy. It is suggested that two different mechanisms are involved.

6. A single injection of insulin produces a fall in the blood cholesterol of rabbits with hypercholesterolemia. If anything, thyroidectomy increases the magnitude of this effect.

BIBLIOGRAPHY

1. Turner, K. B., *J. Exp. Med.*, 1933, **58**, 115.
2. Turner, K. B., and Khayat, G. B., *J. Exp. Med.*, 1933, **58**, 127.
3. Turner, K. B., and Bidwell, E. H., *J. Exp. Med.*, 1935, **62**, 721.
4. Bloor, W. R., Pelkan, K. F., and Allen, D. M., *J. Biol. Chem.*, 1922, **52**, 191.
5. Remond, A., Colombies, H., and Bernardbeig, J., *Compt. rend. Soc. biol.*, 1924, **91**, 445.
6. Baumann, E. J., and Holly, O. M., *Am. J. Physiol.*, 1926, **75**, 618.
7. Kunde, M. M., Green, M. F., and Burns, G., *Am. J. Physiol.*, 1932, **99**, 469.
8. Westra, J. J., and Kunde, M. M., *Am. J. Physiol.*, 1933, **103**, 1.
9. Parhon, C. I., and Ornstein, I., *Bull. Soc. chim. biol.*, 1935, **17**, 1119.
10. Mitani, M., *Folia endocrinol. Japon.*, 1932, **8**, 47. (*Chem. Abstr.*, 1934, **28**, 5514.)
11. Yoshimura, O., *J. Chosen Med. Assn.*, 1931, **21**, 1079. (*Chem. Abstr.*, 1932, **26**, 3830.)
12. Turner, K. B., and Bidwell, E. H., *Proc. Soc. Exp. Biol. and Med.*, 1937, **35**, 656.